REMARKS

Status of the Claims.

Claims 1-11, and 27-37 are pending with entry of this amendment, claims 12-26, and 38-56 being cancelled and no claims being added herein. Claims 1 and 27 are amended herein. These amendments introduce no new matter. Support is replete throughout the specification.

Election/Restriction.

Pursuant to a restriction requirement made final, Applicants cancel claims 12-26, and 38-56 with entry of this amendment. Please note, however, that Applicants reserve the right to file subsequent applications claiming the canceled subject matter and the claim cancellations should not be construed as abandonment or agreement with the Examiner's position in the Office Action.

Information Disclosure Statement.

Applicants note that an Information Disclosure Statement (PTO Form 1449) was submitted on April with appreciation the Examiner's thorough consideration of the references cited in the Information Disclosure Statement (Form 1449) submitted on April 10, 2003 (the same date as the mailing date of the present Office Action). Applicants request that the references cited therein be considered and made of record in the present application.

35 U.S.C. §101.

Claims 1-11 were rejected under 35 U.S.C. §101 as being directed to non-statutory subject matter. The claims as written allegedly encompass a human. Per the Examiner's recommendation, claim 1 is amended herein to read non-human knockout mammal" thereby obviating this rejection.

35 U.S.C. §112, First Paragraph, Description Requirement.

A) Scope of knockout gene.

Claims 1-11 and 27-37 were rejected under 35 U.S.C. §112, first paragraph, as containing subject matter allegedly not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In particular, the Examiner alleged that because the claims are drawn to "a *Ttpa* gene" they encompass any Ttpa gene that may exist (i.e. the Examiner appears to

contemplate the existence of Ttpa genes other than orthologues of the recited gene). It is noted that the Examiner further states "only the Ttpa gene disclosed in the specification and its orthologue in other mammalian species, but not the full breadth of the claims meet the written description provision. . . " (*see* Office Action, page 3, bottom).

For the purposes of clarity, claim 1 is amended herein to recite:

> 1. A viable knockout non-human mammal, said mammal comprising a disruption in **the endogenous α tocopherol transfer protein gene (Ttpa), or its orthologues**, wherein said disruption results in said knockout mammal exhibiting a decreased level of α-tocopherol transfer protein (α-TTP) as compared to a wild-type animal. [emphasis added]

In addition, independent claim 27 is similarly amended. This amendment is consistent with the scope that the Examiner stated meets the description requirement. Accordingly the rejection of claims 1-1 and 27-37 on these grounds should be withdrawn.

B) Scope of animal species.

Claims 1-11 and 27-37 were rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to meet the description requirement. IN particular, the Examiner alleged that knockout animals produced using nuclear transfer methods would produce knockout animals equivalent to those produced using ES cells.

Applicants first respectfully remind the Examiner that the pending claims are directed to the knockout animals themselves, not to methods of making such.

Applicants also note that claims 27-37 are drawn to knockout rodents. ES cells are readily available for rodent species. Moreover, Applicants have demonstrated that Ttpa knockout rodents are viable. One of ordinary skill in the art, reading the specification, would readily conclude that Applicants are in "possession" of Ttpa knockout rodents and the rejection of claims 27-37 on these grounds should be withdrawn.

The Examiner is reminded that "[t]he written description requirement **does not require the applicant 'to describe exactly the subject matter claimed**, [instead] the description must clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed.

[emphasis added] '" *Union Oil Co. v Atlantic Richfield et al.* 208 F.3d 989 (Fed. Cir. 2000) *citing In re Gosteli*, 872 F.2d 1008, 1012, 10 U.S.P.Q.2D (BNA) 1614, 1618 (Fed. Cir. 1989).

In the present case, claim 1 is directed to:

> 1 A viable knockout non-human mammal, said mammal comprising a disruption in the endogenous α tocopherol transfer protein gene (Ttpa), or its orthologues, wherein said disruption results in said knockout mammal exhibiting a decreased level of α-tocopherol transfer protein (α-TTP) as compared to a wild-type animal.

While claim 27 is directed to:

> 27. A viable **knockout rodent** comprising a disruption in ~~an~~ the endogenous α tocopherol transfer protein gene (Ttpa), or its orthologues, wherein said disruption results in said knockout rodent exhibiting decreased levels of α-tocopherol transfer protein (α-TTP) as compared to a wild-type animal.

Applicants have produced knockout mice having a disruption in the *Ttap* gene and showing a viable phenotype. Having demonstrated that *Ttpa* knockout mammals are viable one of ordinary skill in the art would appreciate that Applicants are in possession of the claims invention.

With respect to the Examiner's argument that the art is unpredictable and consequently Applicants have failed to show possession of the claimed genus, it is noted that gene transfer techniques are not necessarily required to produce the claimed animals. Rather they simply provide one of many available approaches. Given that the knockout has been produced, shown to be viable, and shown to have the recited phenotype, the art is no longer unpredictable with respect to *Ttpa* knockouts and the genus is properly and fully described.

In view of these considerations, Applicant believe the Examiner has failed to make his *prima facie* case and the rejection of claims 1-11 and 27-37 under 35 U.S.C. §112 on these grounds should be withdrawn.

35 U.S.C. §112, first paragraph, "make and use" enablement.

Claims 1-11, and 27-37 were rejected under 35 U.S.C. §112, first paragraph, because the specification, is allegedly "not enabling for any species of mammal comprising a disruption in any

Ttpa gene where the disruption is a substitution and where the animal has any phenotype other than a decreased level of alpha-tocopherol transfer protein, vitamin E deficiency, or female infertility."

First, Applicants note that the claims are not directed to a disruption of any Ttpa gene other than the described Ttpa gene and its orthologues.

Second, with respect to the Examiner's comments regarding a substitution, Applicants note that the Examiner indicated that the Application was enabling for a disruption that is an insertion. If the inserted sequence is the same as the Ttpa gene sequence, but for changes in one or several codons, then the **insertion** disruption is, in effect, a **substitution**. Consequently the specification is fully enabling for a disruption that comprises a substitution.

Third, with respect to the Examiner's comment that the specification is not enabling for Ttpa knockouts having any phenotype, it is noted that independent claims 1 and 27 both recite that the knockout animal exhibits: "**decreased levels of α-tocopherol transfer protein (α-TTP) as compared to a wild-type animal.**" The claims are thus clearly limited to a well-defined phenotype.

Finally, the Examiner is reminded that to be enabling under § 112, first paragraph, a "patent need not teach, and preferably omits, what is well known in the art." *See, M.P.E.P.* § 2164.01 *citing Spectra-Physics, Inc. v. Coherent, Inc.*, 3 USPQ2d 1737 (Fed. Cir. 1987). A patent must contain a description that enables one skilled in the art to make and use the claimed invention. That some experimentation is necessary does not constitute a lack of enablement; the amount of experimentation, however, must not be unduly extensive.

Whether undue experimentation is required by one skilled in the art is typically determined by reference to eight factors considered relevant to the inquiry (1) the nature of the invention; (2) the breadth of the claims; (3) unpredictability of the art; (4) the state of the prior art; (5) the presence of working examples; (6) amount of guidance in the specification; (7) the level of skill in the art; and (8) the quantity of experimentation necessary. *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988) *citing Ex parte Forman Inc.*, 230 USPQ 546 (BPIA 1986).

As explained below, when analyzed in light of the standards put forth by the Federal Circuit in *In re Wands*, it is clear that the presently claimed invention can be practiced without undue experimentation.

Nature of the Invention:

The nature of the invention (Wands Factor 1) relates to a knockout or transgenic mammal comprising a disrupted Ttpa gene. Having demonstrated in the present application that *Ttpa* knockout animals are viable, one of ordinary skill in the art can readily produce a knockout mutant using any of a variety of well-known techniques (*e.g.* homologous recombination, RNAi, and the like). *See, e.g.*, Kohara *et al.* (2001) *Curr Biol* 2001 11(3): 171-176 and Barstead (2001) *Curr Opin Chem Biol* 5(1): 63-66 (abstracts previously submitted). The nature of the invention is thus relatively straightforward.

Breadth of the Claims:

Contrary to the Examiner's assertion, the breadth of the claims is relatively narrow. The claims as amended are directed to "a viable nono-human mammal" or "a viable knockout rodent" comprising a disruption in the Ttap gene where the animal exhibits decreased levels of α-tocopherol transfer protein (α-TTP) as compared to a wild-type animal. The claims are thus limited to disruption of a particular gene resulting in a particular phenotype and are therefore relatively narrow.

Unpredictability of the Art and State of the Prior Art

Contrary to the Examiner's assertion, having demonstrated that mammals having a disrupted Ttpa gene are viable and produce decreased levels of α-tocopherol transfer protein (α-TTP), the art is quite predictable. The Examiner has offered no objective evidence to establish that other Ttpa knockouts (*e.g.* with the disruption located in another part of the Ttpa gene) would differ in viability or phenotype. Having demonstrated that the animals are viable when this gene is disabled, the particular location of the knockout within the subject (Ttpa) gene, or the nature of the disruption, is unlikely to alter the outcome.

At the time of filing, both the nucleotide sequence and amino acid sequences of *Ttpa*, and its encoded protein were publicly available, and readily accessible by those of skill in the art. The present invention clearly demonstrates that deletions, both structural and functional disruption of the *Ttpa* gene result in viable organisms. This discovery, in conjunction with the availability of *Ttpa* sequence data, enables those of skill in the art to design and produce structural and/or functional deletions of "any or all," that is, one or more exons of the wild-type *Ttpa* gene and one of ordinary skill would expect all such knockouts to function similarly.

The Examiner has offered no objective basis that would lead one of skill to conclude that the methods disclosed in the present application would require more than routine application to

other mammals. Accordingly, in view of the teachings provided in the specification and the art, the subject matter of the claims is now highly predictable.

Working Examples and Guidance in the Specification:

The specification provides considerably guidance and working examples. In particular, the specification illustrates the creation of Ttpa knockouts.

The Examiner states that "there are no examples or guidance in the specification on how to reliably produce transgenic nematodes other than the exemplified animals." **The Examiner, however, has failed to establish that the methods used and described are inapplicable to other species of mammals**. The Examiner simply ignores the extensive teachings in the specification relating to the production of knockout mutants. Using the teachings provided in the specification in combination with the available sequence data, a practitioner of skill in the art can readily produce essentially any desired knockout of the *Ttpa* gene in any of a number of mammals without undue experimentation.

In addition, the Examiner is reminded that the Federal Circuit has already determined that routine screening, even routine screening of large numbers of moieties for a particular property (*e.g.* antibody libraries for antibodies of particular specificity and/or avidity) is not undue experimentation (*see, e.g., In re Wands, supra.*).

Level of Skill in the Art:

Applicant reminds the Examiner that the level of skill in the art is high (typically Ph.D.). The production of knockout mutantsis a routine technical exercise for practitioners skilled in the art.

Quantity of Experimentation:

Having demonstrated in the present application that *Ttpa* mutants are viable, the production of knockout mutants is a routine technical matter accomplished without undue experimentation by a practitioner skilled in the art. Moreover, the Examiner is reminded that **the Court of Appeals for the Federal Circuit has expressly stated that simple screening (*e.g.* screening of large antibody libraries), is not undue experimentation**:

> Enablement is not precluded by the necessity of some experimentation such as routine screening. However, experimentation needed to practice the

invention must not be undue experimentation. "[T]he key word is 'undue' not 'experimentation'. *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Having demonstrated in the present application that a Tta[knockout mouse is viable, it is a mere technical exercise (*e.g.* screening exercise) to other produce knockout mutants having structural or functional deletions in the wild type *Ttpa* gene.

Conclusion:

When analyzed in light of *In re Wands*, practice of the invention of claims 1-11 and 27-37 **does not** require undue experimentation and the rejection of these claims under 35 U.S.C. §112, first paragraph, should be withdrawn.

35 U.S.C. §112, second paragraph.

Claims 1, 8, 9, 27, 34, and 35 were rejected as allegedly indefinite. In particular the Examiner alleged that claims 1 and 27 are indefinite because recitation of a ". . . disruption in an endogenous Ttpa gene" could refer to multiple Ttpa genes because it encompasses multiple species of animals or because it encompasses multiple Ttpa genes for each species.

The language "an endogenous Ttpa gene" is intended to refer simply to the Ttpa gene and its orthologues (as made express in the pending claims). It is noted that use of the article "an" is consistent with standard patent practice (often an initial occurrence of "the" is rejected for lack of antecedent basis). Nevertheless to facilitate procecution, Applicants have amended claims 1 and 27 to improve clarity and obviate this rejection.

Claims 8, 9, 34, and 35 were rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite because they encompass animals wherein the gene disruption "is **only** in somatic cells", or "only in germ cells". Applicants submit the Examiner has failed to properly read the claims at issue. **Nowhere in the claims is there a limitation that the disruption is only in somatic cells or only in germ cells.** Claims 8 and 9, for example simply make clear that the disruption is in **a** germ cell or **a** somatic cell of the animal.

With respect to the Examiner's assertion that "all" cells in an animal must carry the disruption is simply incorrect. Once a knockout has been shown to be viable chimeric animals (*e.g.* calico mice) can routinely be produced containing, *e.g.* wildtype cells and cells containing the disruption. Similarly, once a viable knockout has been produced, the animals can be inbred or outbred to produce animals homozygous or heterozygous for the knockout.

With respect to the alleged lack of clarity with respect to a recitation of "a cell", Applicants submit that the Examiner has failed to read the claim in accordance with common patent usage. The phrase "a cell" means exactly what it says. "A cell" simply refers to "a cell" it does not refer to "one cell". The phrase "one cell" is a limitation not present in the claims.

35 U.S.C. §102(a).

Claims 1-5, 8-11, 27-31, and 34-37 were rejected under 35 U.S.C. §102(a) as allegedly anticipated by Terasawa (Nov. 2, 1999) *Circulation*, 100: 1-46. Applicants traverse.

The priority date of the present application is November 2, 2000. The publication date of the cited reference is November 2, 1999. Accordingly the cited reference is not published more than a year prior to the filing date of the present application and the reference is only available under 35 U.S.C. §102(a).

Upon a showing of otherwise allowable subject matter, Applicants will provide a Katz declaration eliminating this reference as prior art.

35 U.S.C. §103(a).

Claims 1-5, 8-11, 27-31, and 34-37 were rejected under 35 U.S.C. §103(a) as allegedly obvious in light of Capecchi (1994) Scientific American, 270: 34-41 in view of Fechner (1999) GenBank Accession No: AF218/416. The Examiner alleged that Capecchi taught a mouse whose genome comprised a disruption in the HoxA-3 gene by insertion of a selective marker into that gene, while Fechner taught the nucleic acid sequence of the mouse *Ttpa* gene and Ttpa coding region. The Examiner further alleged one of skill would have been motivated to disrupt the Ttpa gene (substitute Ttpa for HoxA-3) to generate an animal model of Vitamin E deficiency. Applicants traverse.

A *prima facie* case of obviousness requires that the combination of the cited art, taken with general knowledge in the field, must provide all of the elements of the claimed invention. When a rejection depends on a combination of prior art references, there must be some teaching, suggestion, or motivation to combine the references. *In re Geiger*, 815 2 USPQ2d 1276, 1278 (Fed. Cir. 1987). Moreover, to support an obviousness rejection, the cited references must additionally provide **a reasonable expectation of success**. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991), *citing In re Dow Chemical Co.*, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988).

A) There is no reasonable expectation of success.

In the instant case, claims 1 and 27, as amended herein, are directed to "[a] **viable** knockout non-human mammal". As recognized by the Examiner the art of making knockout animals is unpredictable. Moreover, there is nothing in the art cited by the Examiner that leads on of skill to conclude that Ttpa knockout animals are capable of coming to term, surviving and growing.

Until Applicants demonstrated that the *Ttpa* gene could be knocked out and still produce a viable animal **there was no reasonable expectation of success** that viable *Ttpa* knockouts could be produced. Accordingly, the Examiner has failed to make her *prima facie* case of obviousness and the rejection of claims 1-5, 8-11, 27-31, and 34-37 on these grounds should be withdrawn.

B) It is improper to consider method of making the animals.

In formulating her rejection, the Examiner improperly considered the method of making the claimed animals. In effect, the Examiner alleged that because **methods** to make a HoxA-3 gene knockout were known and the Ttpa sequence was known, the particular claimed Ttpa knockout animals would have been obvious in light of these methods. The courts have specifically rejected this basis for rejecting claims (*see In re Bell* 26 USPQ2d 1529 (Fed. Cir. 1994) and *In re Deuel* 34 USPQ2d 1210 (Fed. Cir. 1995)). In both cases, the PTO alleged that composition claims (in those cases directed to nucleic acids) were obvious in view of references that taught general methods for making oligonucleotides and then using them to isolate desired nucleic acids. In *Deuel*, the Federal Circuit reversed the PTO, reasoning that:

> The PTO's focus on known methods for potentially isolating the claimed DNA molecules is also misplaced because the claims at issue define compounds, not methods. . . . **We today reaffirm the principle, stated in *Bell*, that the existence of a general method of isolating cDNA or DNA molecules is essentially irrelevant to the question whether the specific molecules themselves would have been obvious, in the absence of other prior art that suggests the claimed DNAs.** [emphasis added] *Deuel*, 51 F.3d at 1555.

Here, as in *Bell* and *Deuel*, the Examiner argues that the claimed knockout animals are obvious in light of a general method for making knockouts and an alleged disclosure of the Ttpa gene.. The Examiner has failed to show how the cited references provide any specific information about the

particular claimed knockout animals. To the contrary, the cited references provide no teaching or suggestion of Ttpa knockout animals, and no indication of the use of such animals. Furthermore, the cited art not only fails to teach or suggest Ttpa knockout animals, but also fails to teach or provide a reasonable expectation that such Ttpa knockout animals are viable.

Since the cited references neither disclose nor suggest the existence of the particular claimed knockout animals and the Federal Circuit has stated that consideration of a general method of discovery is an improper basis for an obviousness rejection, Applicants submit the Examiner has failed to make her *prima facie* case. Accordingly, the rejection of claims 1-5, 8-11, 27-31, and 34-37 under 35 U.S.C. §103(a) should be withdrawn.

In view of the foregoing, Applicants believes all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. Should the Examiner seek to maintain the rejections, Applicants request a telephone interview with the Examiner and the Examiner's supervisor.

If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (510) 769-3513.

QUINE INTELLECTUAL PROPERTY LAW
GROUP, P.C.
P.O. BOX 458
Alameda, CA 94501
Tel: 510 337-7871
Fax: 510 337-7877

Respectfully submitted,

Tom Hunter
Reg. No: 38,498